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(12) # EUROPEAN PATENT SPECIFICATION

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(54) **2-Substituted 4-amino-6,7-dimethoxyquinolines.**

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EP-A-0 028 473
EP-A-0 047 923
DE-A-2 006 638
GB-A- 890 533
GB-A-1 010 254

CHEMICAL ABSTRACTS, vol. 88, no. 1, January 2, 1978, Columbus, Ohio, USA, R.N. BROGDEN, "Prazosin: a review of its pharmacological properties and therapeutics efficacy in hypertension", page 1, abstract no. 6y

The file contains technical information submitted after the application was filed and n t included in this specification

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(56) References cited:
CHEMICAL ABSTRACTS, vol. 95, no. 1, July 6, 1981, Columbus, Ohio, USA, V.E. GOLUBEV, "Synthesis and pharmacological properties of some 1-(2-quinolyl)-4-(indolyl-3-alkyl)-piperazines", page 685, abstract no. 7218x
Burger's Medicinal Chemistry, Part I, Wiley-Interscience, New York, 1951, pages 74-76

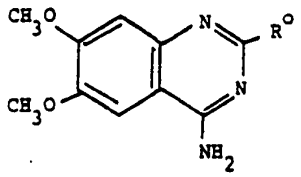
Courier Press, Leamington Spa, England.

EP 0 100 200 B1

Description

This invention relates to therapeutic agents which are novel derivatives of 4-amino-6,7-dimethoxyquinoline. Such compounds are useful as regulators of the cardiovascular system and, in particular, in the treatment of hypertension.

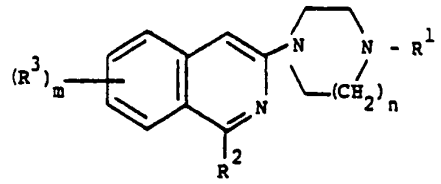
Quinazoline derivatives of the formula:—



--- (A)

in which R° represents a wide variety of substituted amino groups, including cyclic amino groups, are known as antihypertensive agents, as disclosed in U.S. Patent 3511836 and other U.S. Patents, as referred to in, for example, European published application 0028473.

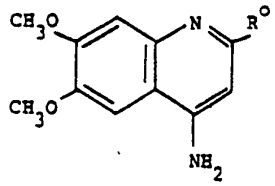
*Iso*quinoline derivatives of the formula:—



--- (B)

in which R^1 and R^3 have a variety of meanings, but R^2 can only be hydrogen or an alkyl group, are also known as antihypertensive agents from European published application 0047923.

However, quinoline derivatives of the formula:—



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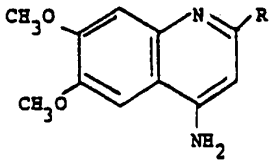
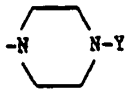
analogous to the quinazoline derivatives of formula (A) are not known and no method for their preparation has yet been described.

The novel compounds according to the invention are those having the formula:—



--- (I)

and their pharmaceutically acceptable acid addition salts, wherein R is —N(C_1—C_4 alkyl)$_2$, piperidino, 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinol-2-yl or a group of the formula



wh re Y is H, C_1—C_6 alkyl, aryl or C_1—C_4 alkyl substituted by aryl, or Y is selected from

(a) —COR^1 where R^1 is a C_1—C_6 alkyl, C_1—C_4 alkyl substituted by aryl, C_3—C_6 cycl alkyl, (C_3—C_6 cycloalkyl)methyl, aryl, styryl, 2-furyl, 2-tetrahydrofuryl, 2-benzo-1,4-dioxanyl, 2-chromanyl, 5-methylthio-2-(1,3,4-oxadiazolyl) or 2-quin lyl group;

(b) —CONHR^2 where R^2 is C_1—C_6 alkyl, aryl, C_1—C_4 alkyl substitut d by aryl, (C_2—C_4 alkenyl)methyl, C_3—C_6 cycl alkyl or (C_3—C_6 cycloalkyl)methyl; and

(c) —COOR^3 wher R^3 is C_1—C_6 alkyl substituted by aryl, C_2—C_4 alkyl substituted other than on an α-carbon

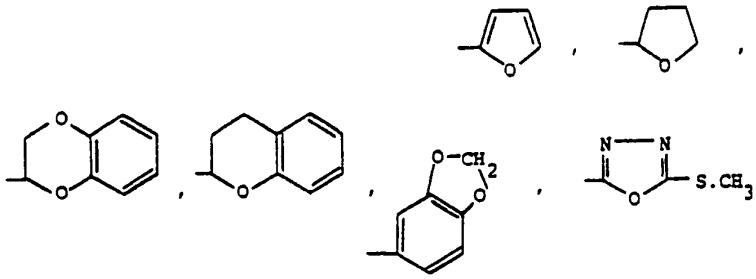
atom by hydroxy, C_3—C_6 cycloalkyl, (C_3—C_6 cycloalkyl)methyl, (C_2—C_4 alkenyl)methyl, or aryl; wherever it occurs, the term "aryl" means phenyl, naphthyl, or phenyl substituted by 1 or 2 substituents each selected from halo, CF_3, C_1—C_4 alkyl and C_1—C_4 alkoxy, or by a single methylenedioxy group.

"Halo" means F, Cl, Br or I.

Alkyl, alkoxy and alkenyl groups can be straight or, when appropriate, branched chain. Preferred alkyl groups have 1 to 4 carbon atoms.

Pharmaceutically acceptable acid addition salts of the compounds of the invention are those formed from acids which form non-toxic acid addition salts containing pharmaceutically acceptable anions, such as the hydrochloride, hydrobromide, sulphate or bisulphate, phosphate or acid phosphate, acetate, maleate, fumarate, succinate, lactate, tartrate, citrate, gluconate and p-toluenesulphonate salts.

Examples of R^1 include



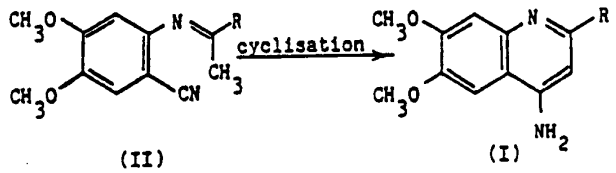
phenyl, *p*-fluorophenyl, methyl, cyclopropylmethyl, cyclopentyl, styryl, 2-naphthyl and 2-quinolyl.

Examples of R^2 include phenyl, cyclopropylmethyl, benzyl, *n*-propyl and allyl.

Examples of R^3 include ethyl, $—CH_2CH(CH_3)_2$, $—CH_2C(CH_3)_2(OH)$, cyclopropylmethyl, *p*-fluorophenyl, benzyl and $—CH_2.C(CH_3)=CH_2$.

The compounds of the formula (I), can be prepared as follows:—

(1) An N-(1R-substituted-ethylidene)-2-cyano-4,5-dimethoxy-aniline (II) may be cyclised to form the correspondingly substituted 4-amino-6,7-dimethoxyquinoline (I):—

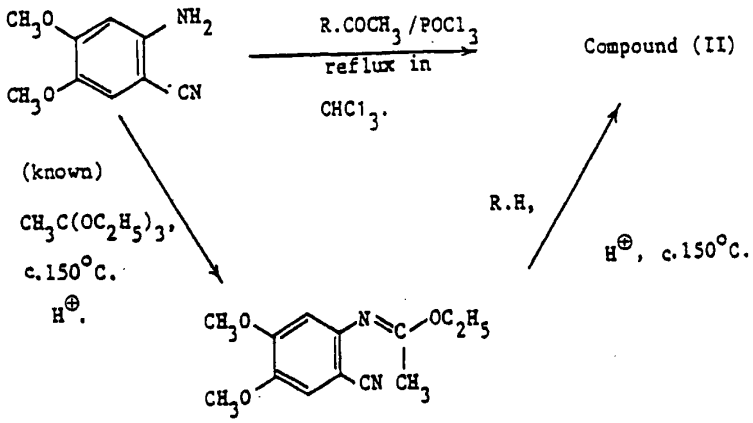


(II) (I)

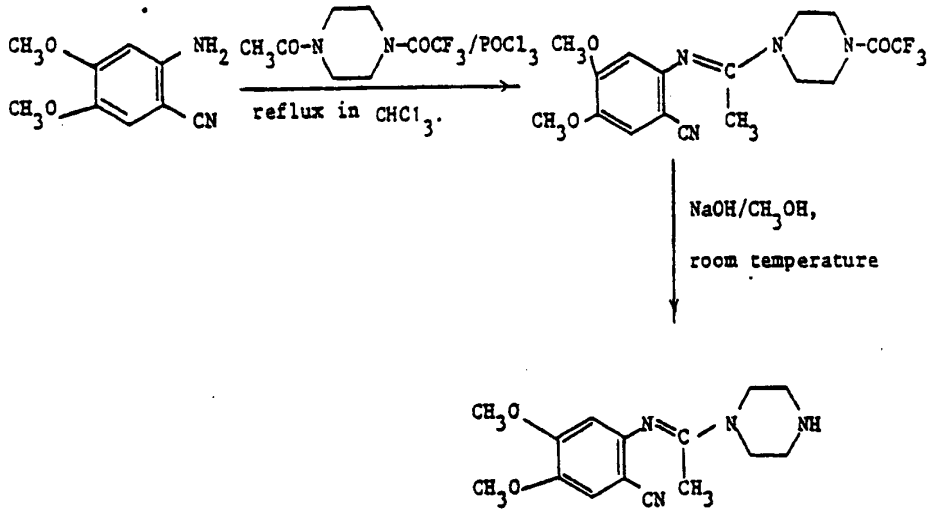
The cyclisation can be carried out using a Lewis acid, e.g. zinc chloride, or a base, e.g. lithium diisopropylamide (LDA). Zinc chloride is preferred when R is said tetrahydroisoquinolyl group or an N-aralkyl-piperazino group. The reaction with zinc chloride is typically carried out by heating the reactants, preferably at reflux, in a suitable organic solvent, e.g. dimethylacetamide for up to about 4 hours. The reaction with LDA is typically carried out at low temperature (e.g. −70°C) in a suitable organic solvent, e.g. tetrahydrofuran, following which the reaction mixture is allowed to warm to room temperature. In some cases using LDA, heating may be necessary to complete the reaction. The product can then be isolated and purified conventionally.

The compounds (II) are obtainable conventionally as is illustrated in the following Preparations. Typical methods are outlined as follows:—

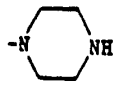
(a) For compounds where R is as defined above except for unsubstituted piperazinyl (Y = H):—



(b) For compounds in which R is unsubstituted piperazinyl:—

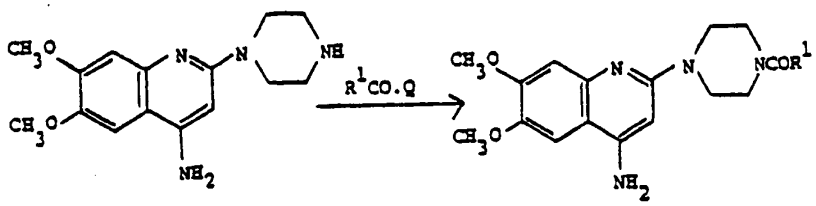


(2) The Compound in which R is



can also be prepared by debenzylation of the corresponding 4-benzylpiperazin-1-yl compound, itself preparable via route (1) above. This can be carried out conventionally using, e.g., H_2 over a Pd/C catalyst.

(3) Compounds in which Y is —COR^1 can be prepared as follows:—

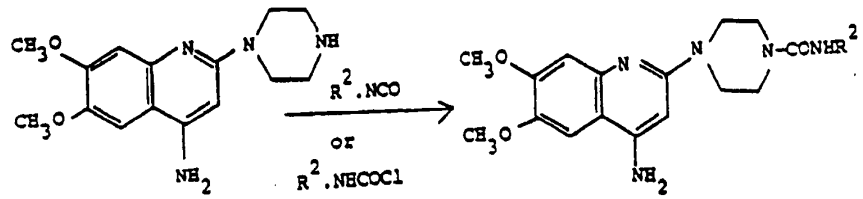


Q is a facile leaving group, preferably Cl.

The reacti n can be carried out conventionally. When Q is Cl, the presence f a tertiary amine acid acceptor such as tri thylamine is desirable. Gen rally, heating is unn cessary. Typically the reactants are

stirred together in a suitabl organic solvent, e.g. chloroform, at 5—10°C for 1—2 hours. Th reaction mixture can then be allowed to attain room temperature and the product isolated conventionally.

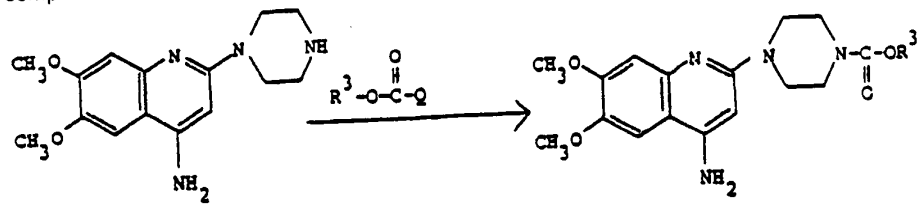
(4) Compounds in which Y is —CONHR^2 can be prepared as follows:—



When an isocyanate R^2.NCO is used, the reaction can again be carried out conventionally, e.g. by stirring the reactants together for a few hours (e.g. 3—6 hours) in a suitable organic solvent, e.g. chloroform. Heating is again generally unnecessary; the product can be isolated routinely.

When a carbamoyl chloride R^2.NHCOCl is used, this may be generated *in situ* by the action of phosgene on the amine R^2.NH$_2$ as its hydrochloride salt in the presence of an acid acceptor such as triethylamine in a dry, cooled organic solvent, such as chloroform at −40°. After allowing this to warm to ambient temperature and removing excess phosgene, a solution of the piperazino-quinoline in the same solvent is added slowly with cooling, the mixture stirred until reaction is complete and the product isolated routinely.

(5) Compounds in which Y is —COOR^3 can be prepared as follows:—



where Q is a facile leaving group, preferably Cl. Typically the reaction is carried out by stirring the reactants together for a few hours in a suitable organic solvent such as chloroform, preferably, when Q is Cl, in the presence of an acid acceptor such as triethylamine. Heating is not generally necessary, and the product can be isolated in a routine manner.

Certain compounds of the invention can be converted to other compounds of the invention by conventional means and an alkenyl-methyl group R^3 can be converted to a hydroxyalkyl-methyl group by treatment with concentrated sulphuric acid, as is also well known in the art.

The pharmaceutically acceptable acid addition salts of the compounds of the formula (I) can be prepared by conventional procedures, e.g. by reacting the free base with the appropriate acid in an inert organic solvent, and collecting the resulting precipitate of the salt by filtration or by evaporation of the reaction mixture. If necessary, the product may then be recrystallised to purify it.

When the compounds of the invention contain an asymmetric centre, the invention includes both the resolved and unresolved forms. Resolution of optically active isomers can be carried out according to conventional prior art methods.

The antihypertensive activity of the compounds of the formula (I) is shown by their ability to lower the blood pressure of conscious spontaneously hypertensive rats and conscious renally hypertensive dogs, when administered orally at doses of up to 5 mg/kg.

The compounds of the formula (I) and their salts can be administered alone, but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they can be administered orally in the form of tablets containing such excipients as starch or lactose, or in capsules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavouring or colouring agents. They can be injected parenterally, for example, intramuscularly, intravenously or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other solutes, for example, enough salt or glucose to make the solution isotonic.

Thus the invention also provides a pharmaceutical composition comprising a compound of the formula (I) or pharmaceutically acceptable acid addition salt thereof together with a pharmaceutically acceptable diluent or carrier.

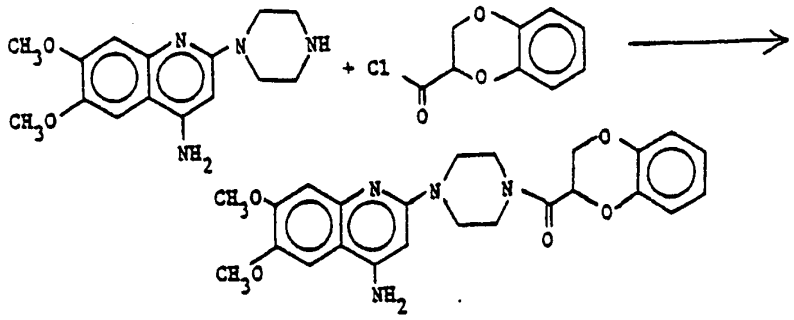
It als pr vides a c mpound of th f rmula (I), or a pharmaceutically acceptable acid addition salt there f, for use in tr ating hypertension in a human being.

The compounds of the formula (I) and their salts can be administered t humans for the treatment of hypert nsion by either the oral or parenteral r utes, and will be administered orally at dosage levels within th range 1 t 50 mg/day for an average adult patient (70 kg), given in a single dose or up t 3 divided d s s. Intraven us dosage levels will be ½th to ¼₀th of th daily oral dose. Thus for an average adult

patient, individual oral doses in tablet or capsule form will be approximately in the range from 1 to 25 mg of the active compound. It should however be stated that variations will necessarily occur depending on the weight and condition of the subject being treated and the particular route of administration chosen as will be known to those skilled in the art.

The following Examples illustrate the invention. All temperatures are in °C:—

Example 1



A solution of 1,4-benzodioxan-2-carbonyl chloride (0.75 g) in chloroform (10 ml) was added dropwise to a stirred solution of 4-amino-6,7-dimethoxy-2-(piperazin-1-yl)quinoline (1.0 g) in chloroform (50 ml) with triethylamine (1.06 g) at 5—10°. The reaction was stirred at 5—10° for one hour, then allowed to attain room temperature and stirred overnight. The mixture was then evaporated *in vacuo* and the residue partitioned between chloroform (50 ml) and sodium carbonate solution (10%, 50 ml). The chloroform layer was separated, the aqueous phase extracted with chloroform (2 × 50 ml), the extracts combined, washed with brine, dried (Na_2SO_4) and evaporated *in vacuo*. The residue was then taken up in chloroform and chromatographed on silica (Merck 9385, 60 g) eluting with chloroform/methanol (100:0→97:3). A solution of the purified product in chloroform was treated with ethereal hydrogen chloride, evaporated *in vacuo* and the residue recrystallised from isopropanol to give 4-amino-2-[4-(1,4-benzodioxan-2-carbonyl)piperazin-1-yl]-6,7-dimethoxyquinoline hydrochloride hydrate (0.28 g), m.p. 201°.

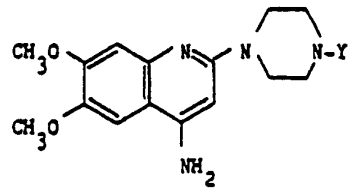
Analysis %:—

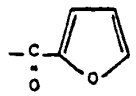
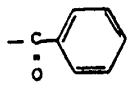
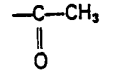
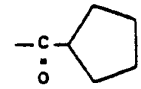
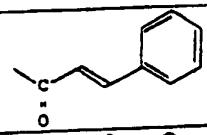
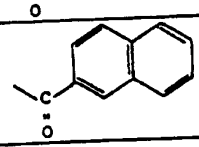
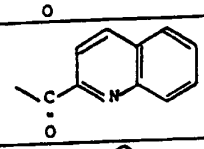
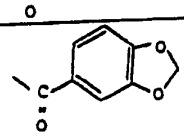
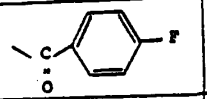
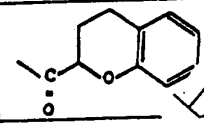
Found: C, 56.7; H, 5.4; N, 11.0

Calculated for $C_{24}H_{26}N_4O_5.HCl.H_2O$: C, 57.1; H, 5.8; N, 11.1.

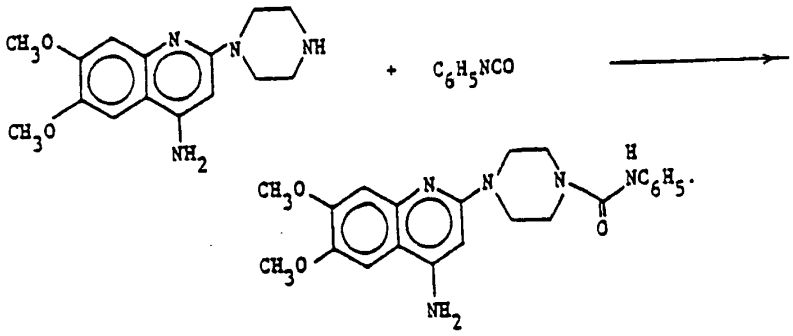
Examples 2 to 11

The following compounds were prepared similarly to Example 1, starting from the same quinoline and the appropriate acid chloride as indicated. After chromatography, the product was crystallised from the solvent shown in each case.



Example No.	Y	Form Isolated and m.p. (°C)	Prepared from, and recrystallised from	Analysis % (Theoretical in brackets) C	H	N
2		Hydrochloride 1/4 hydrate, 270°	2-furoyl chloride, MeOH/Et_2O	56.7 (56.7	5.5 5.6	13.5 13.2)
3		Hydrochloride ½ hydrate 301°	benzoyl chloride, MeOH	60.2 (60.3	5.7 6.0	12.7 12.8)
4		HCl. 1.5 H_2O, 215—220°C	Acetyl chloride, (i) EtOH (ii) MeOH/EtOH	52.1 (51.8	6.5 6.7	14.1 14.2)
5		HCl, 292°C	Cyclopentane carbonylchloride, IPA/MeOH 4:1	59.8 (59.9	7.0 6.9	13.5 13.3)
6		HCl. 0.5 H_2O, 240—241°C	cinnamoyl chloride EtOH	61.8 (62.1	6.0 6.1	12.0 12.1)
7		HCl. 0.5 H_2O, > 300°C	2-naphthoyl chloride, MeOH/Et_2O	64.3 (64.0	5.8 5.8	11.6 11.5)
8		HCl. 1.5 H_2O, 238—239°C	Quinoline-2-carbonyl chloride EtOH/MeOH 1:1	59.3 (59.2	5.4 5.8	13.9 13.8)
9		HCl. 0.5 H_2O, 300—301°C	Piperonoyl chloride, MeOH	57.2 (57.3	5.4 5.4	11.6 11.6)
10		HCl. 274°C	*p*-Fluorobenzoyl chloride, hexane IPA	58.5 (59.1	5.7 5.4	12.3 12.5)
11		HCl. H_2O 251—252°C	chroman-2-carbonylchloride, IPA	59.6 59.7	5.9 6.2	11.2 11.1)

Example 12



Phenylisocyanate (1.1 g) was added to a stirred suspension of 4-amino-6,7-dimethoxy-2-(piperazin-1-yl)quinoline (0.72 g) in chloroform (25 ml) at room temperature and the reaction mixture was stirred for 4 hours. The mixture was evaporated *in vacuo*, the residue taken up in methanol-chloroform and treated with ethereal hydrogen chloride. The crude product was purified by chromatography on silica gel eluting with methylene chloride followed by chloroform/methanol and then recrystallised from methanol/ether to give 4-amino-6,7-dimethoxy-2-[4-(N-phenylcarbamoyl)piperazin-1-yl]quinoline dihydrochloride (0.18 g), m.p. 235°.

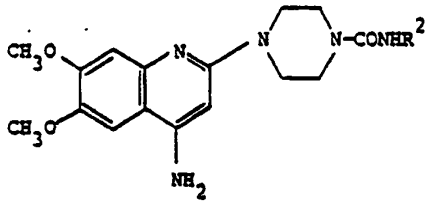
Analysis %:—

Found: C, 55.1; H, 5.7; N, 14.7

Calculated for $C_{22}H_{25}N_5O_3 2HCl$: C, 55.0; H, 5.7; N, 14.6.

Examples 13 to 15

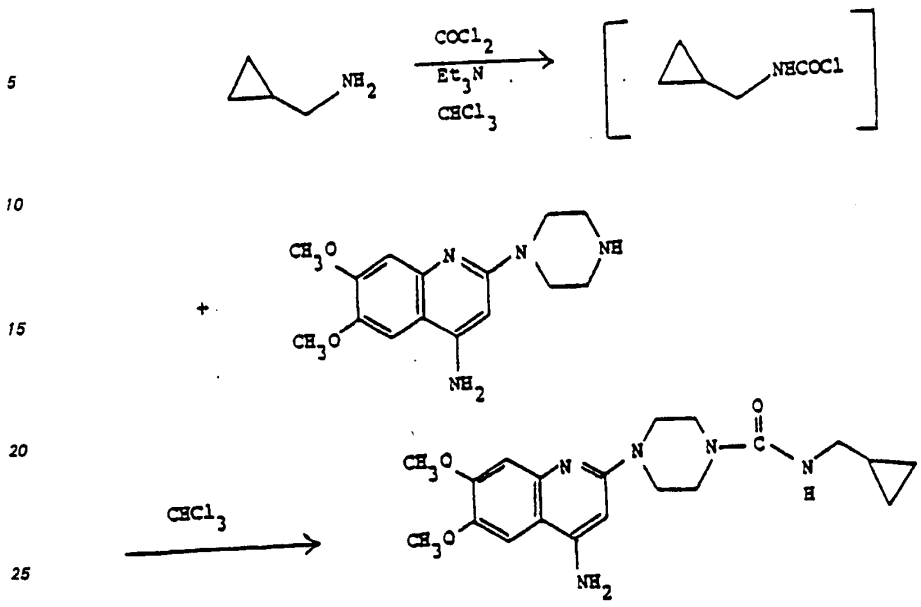
The following compounds were prepared similarly to Example 12, using the appropriate isocyanate $R^2.NCO$ as indicated, and the product crystallised from the solvent shown in each case.



In Example 13 chromatography was not necessary, while in Examples 14 and 15 the reaction mixtures were purified as in Example 16, i.e. chromatographed as the free base and (in the case of Example 14) then converted to the hydrochloride.

Example No.	R^2	Form isolated and m.p. (°C)	Prepared from, and recrystallised from	Analysis % (Theoretical in brackets) C	H	N
13	$-CH_2CH_2CH_3$	HCl. 1.5 H_2O 200° (d)	*n*-propyl isocyanate, MeOH/Et_2O	54.0 (54.5	6.8 7.0	16.7 16.7)
14	$-CH_2C_6H_5$	HCl, 269—270°C	Benzyl isocyanate, IPA	59.8 (60.3	6.1 6.2	14.9 15.3)
15	$-CH_2CH=CH_2$	H_2O, 178—181°C (d)	Allyl isocyanate, EtOAc/CH_2Cl_2/ hexane	58.3 (58.6	6.7 7.0	17.8 18.0)

Example 16



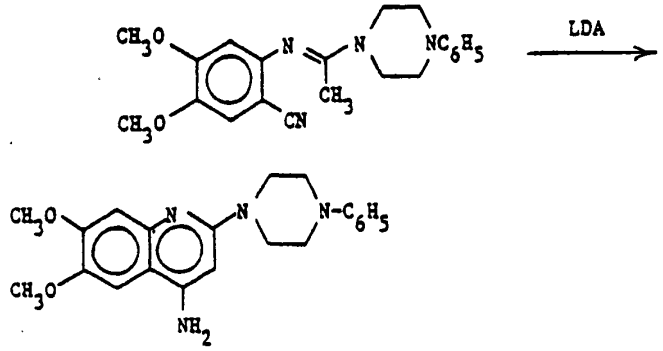
(Aminomethyl)cyclopropane hydrochloride (0.25 g) and triethylamine (0.61 g) in P_2O_5-dried chloroform (15 ml) was added dropwise to a stirred solution of phosgene in toluene (12.5%, 2.6 ml) at −40°. The reaction mixture was allowed to warm to room temperature and stirred for 0.5 hours. Excess phosgene was removed in a steam of nitrogen then a solution of 4-amino-6,7-dimethoxy-2-(piperazin-1-yl)quinoline (0.3 g) in P_2O_5-dried chloroform (30 ml) was added dropwise at 10° and the reaction mixture stirred at room temperature for 1.5 hours. Sodium carbonate solution (10%, 10 ml) was then added and the chloroform layer separated. The aqueous phase was extracted with chloroform, the organic phases combined, washed with water, dried ($MgSO_4$) and evaporated *in vacuo*. The residue was then taken up in methylene chloride and chromatographed on silica (Merck 9385, 85 g) eluting with methylene chloride/methanol (100:0→85:15). A solution of the purified product in methylene chloride was treated with ethereal hydrogen chloride, evaporated *in vacuo* and the residue recrystallised from isopropanol to give 4-amino-2-[4-(N-cyclopropylmethylcarbamoyl)piperazin-1-yl]-6,7-dimethoxyquinoline hydrochloride hemihydrate (165 mg), m.p. 220—223° (d).

Analysis %:—

Found: C, 55.6; H, 6.5; N, 16.4

Calculated for $C_{20}H_{27}N_5O_3 . HCl.0.5\ H_2O$: C, 55.7; H, 6.8; N, 16.3.

Example 17



N-[1-(4-Phenylpiperazin-1-yl)ethylidene]-2-cyano-4,5-dimethoxyaniline (2.5 g) in tetrahydrofuran (35 ml) was added to a stirred solution of lithium diisopropylamid [from *n*-butyl lithium 1.3M in h xan

(6.44 ml) and diisopropylamine (1.44 ml)] in tetrahydrofuran (5 ml) at −70°. The resulting solution was stirred at −70° for 4 hours then allowed to attain room temperature overnight. The mixture was poured into ice-water (100 ml), extracted with chloroform (3 × 200 ml), the combined extracts washed with water, dried (Na_2SO_4) and evaporated *in vacuo*. The residue was taken up in chloroform/methanol, treated with ethereal hydrogen chloride and recrystallised from methanol to give 4-amino-6,7-dimethoxy-2-[4-phenylpiperazin-1-yl]quinoline dihydrochloride hemihydrate (0.82 g) m.p. 288—290°.

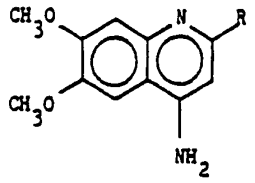
Analysis %:—

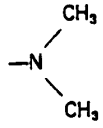
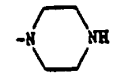
Found: C, 56.9; H, 6.0; N, 12.7

Calculated for $C_{21}H_{24}N_4O_2HCl.\frac{1}{2}H_2O$: C, 56.5; H, 6.1; N, 12.6.

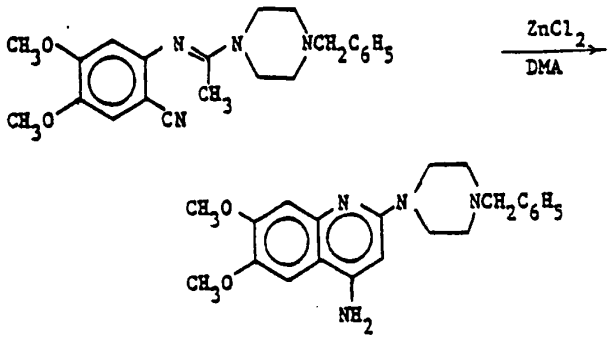
Examples 18 to 20

The following compounds were prepared by the same general route as in Example 17, using the appropriate substituted ethylidene compound of formula (II), except that in Example 19 the reaction was completed by heating on a steam bath. In Examples 18 and 20, the crude product was purified by column chromatography.



Example No.	R	Form Isolated m.p.	Analysis % (Theoretical in brackets) C	H	N
18		HCl, 272—275°	58.9 (59.3	6.9 6.9	13.1 13.0)
19		HCl. $\frac{1}{2}H_2O$ 285—288°	53.8 (53.3	6.3 6.5	14.6 14.4)
20		2HCl. $\frac{1}{2}H_2O$ 260°	47.8 (47.5	6.0 6.4	15.1 14.8)

Example 21



N-[1-(4-Benzylpiperazin-1-yl)ethylidene]-2-cyano-4,5-dimethoxyaniline (13.5 g) and zinc chloride (4.86 g) in dimethylacetamide (90 ml) were stirred under reflux for 2½ hours; further zinc chloride (0.5, 0.2 g) was added after ½ and 1½ hours respectively. The mixture was cooled, treated with ether (700 ml, 2 × 100 ml) and the supernatant discarded each time. The residual tar was then treated with sodium hydroxid

solution (2N, 100 ml) and methylene chloride (100 ml) and the mixture was stirred at room temperature for 5 minutes. The organic layer was separated, the aqueous phase extracted with methylene chloride and the total organic extracts washed with water. The dried (Na_2SO_4) extracts were evaporated *in vacuo* and the brown residue (~ 13 g) purified by chromatography on silica gel (Merck 9385, 250 g) eluting with chloroform-methanol (100:0→88:12). A sample of the pure product (6.95 g) was taken up in ethanol, treated with ethereal hydrogen chloride and evaporated *in vacuo*. The residue was recrystallised from methanol to give 4-amino-6,7-dimethoxy-2(4-benzylpiperazin-1-yl)quinoline dihydrochloride sesquihydrate, m.p. 260°—263°.

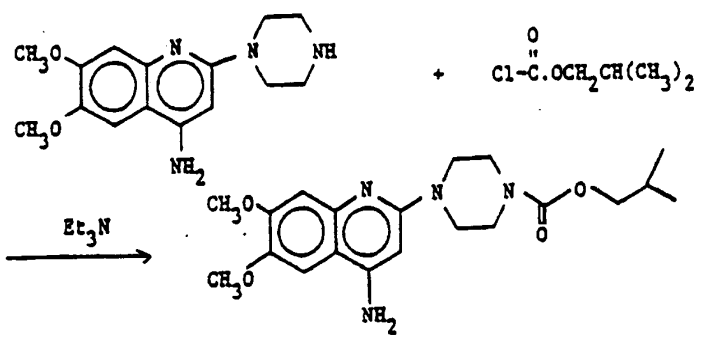
Analysis %:—
Found: C, 54.9; H, 5.9; N, 11.5
Calculated for $C_{22}H_{26}N_4O_2.2HCl.1\frac{1}{2}H_2O$: C, 55.2; H, 6.5; H, 11.7.

Example 22

4-Amino-6,7-dimethoxy-2-[6,7-dimethoxy-1,2,3,4-tetrahydroisoquinol-2-yl]quinoline, m.p. 226—227° was prepared in the same general manner as the previous Example using the corresponding 1-[6,7-dimethoxy-1,2,3,4-tetrahydrosioquinol-2-yl]ethylidene compound except that the crude reaction residue was recrystallised from isopropanol.

Analysis %:—
Found: C, 66.0; H, 6.3; N, 10.9
Calculated for $C_{22}H_{25}N_3O_4$: C, 66.8; H, 6.4; N, 10.6.

Example 23

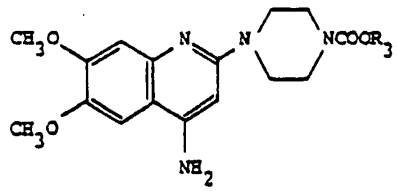


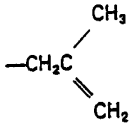
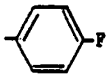
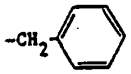
A solution of isobutylchloroformate (0.11 g) in chloroform (5 ml) was added dropwise to a stirred solution of 4-amino-6,7-dimethoxy-2-[piperazin-1-yl]quinoline (0.21 g) in chloroform (15 ml) with triethylamine (0.22 g) at 10°. The solution was then stirred at room temperature for 1 hour and sodium carbonate solution (10%, 10 ml) added. The organic phase was separated, the aqueous solution extracted with chloroform (2 × 15 ml) and the total combined extracts dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by chromatography on silica gel (Merck 9385, 25 g) eluting with methylene chloride-methanol (100:0→93:7), followed by treatment of the product with ethereal hydrogenchloride and recrystallisation from isopropanol to give 4-amino-6,7-dimethoxy-2-[4-(isobutoxycarbonyl)- piperazin-1-yl] quinoline hydrochloride sesquihydrate, m.p. 254—256° (0.065 g).

Analysis %:—
Found: C, 52.8; H, 6.9; N, 12.2
Calculated for $C_{20}H_{28}N_4O_4.HCl.1\frac{1}{2}H_2O$: C, 53.2; H, 7.1; N, 12.4

Examples 24 to 27

The following compounds were prepared similarly to Example 23, using the appropriate chloroformate $ClCOOR_3$ as indicated, the product being crystallised from the solvent shown in each case. The compound of Example 26 was obtained as a bi-product from Example 25, ethyl chloroformate having been formed *in situ* due to traces of ethanol in the chloroform reaction solvent.



Example No.	R^3	Form Isolated and m.p. (°C)	Prepared from, and recrystallised from	Analysis % (Theoretical in brackets) C	H	N
24		HCl H_2O, 244—245°C dec.	2-methylallyl chloroformate (1), IPA	54.8	6.2	12.7
				(54.5	6.6	12.7)
25	$-CH_2CH_3$	HCl 0.5 H_2O, 278—279°C	Ethyl chloroformate (2), IPA	53.5	6.3	13.8
				(53.5	6.5	13.8)
26		HCl, 285°C	*p*-Fluorophenyl chloroformate, MeOH	56.9	5.2	12.1
				(57.1	5.2	12.1)
27		HCl 1.5 H_2O, 204—206°C dec.	Benzyl chloroformate, MeOH	57.2	5.8	12.0
				(56.8	6.2	11.5)

(1) Prepared *in situ*. (2) Formed *in situ*.

Example 28

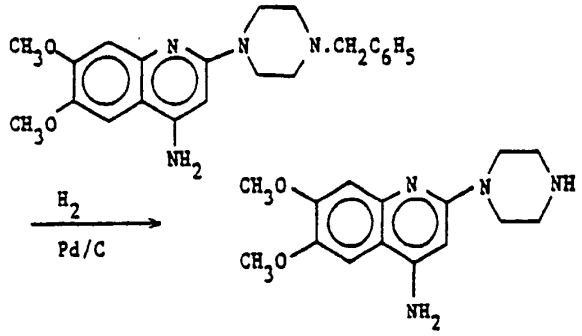
2-Methylallyl 4-[4-amino-6,7-dimethoxyquinolin-2-yl]piperazine-1-carboxylate (0.21 g) was added to a stirred solution of concentrated sulphuric acid (2 ml) and H_2O (2 ml) at 10—15° and stirring maintained at 10—15° for 3 hours. The reaction mixture was basified with sodium hydroxide solution (5N) whilst maintaining temperature below 15° and then extracted with methylene chloride. The combined extracts were washed with water, dried ($MgSO_4$) and evaporated *in vacuo*. Chromatography on silica (Merck 9385, 100 g) eluting with methylene chloride/methanol (100:0 → 85:15) followed by treatment of the product with ethereal hydrogen chloride and recrystallisation from isopropanol gave 2-methyl-2-hydroxypropyl 4-[4-amino-6,7-dimethoxyquinolin-2-yl]piperazine-1-carboxylate hydrochloride hemihydrate (0.05 g), m.p. 280°.

Analysis %:—

Found: C, 53.6; H, 6.6; N, 12.7

Calculated for $C_{24}H_{28}N_4O_6.HCl.0.5\ H_2O$: C, 53.4; H, 6.7; N, 12.5.

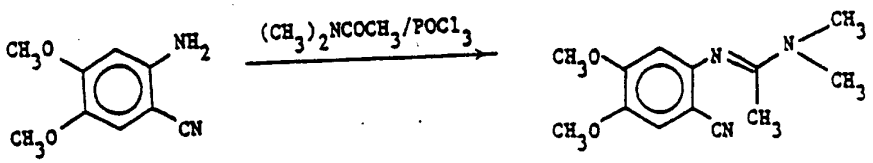
Example 29



4-Amino-6,7-dimethoxy-2-(4-benzylpiperazin-1-yl)quinoline (6.2 g) in ethanol (300 ml) with 5% Pd/C catalyst was stirred at 50° under an atmosphere of hydrogen (50 p.s.i.) for 20 hours. The mixture was cooled, chloroform (100 ml) added and the solution filtered through "Solkafloc" (trade mark). The solid was washed with chloroform-methanol (1:1, 4 × 100 ml) and the combined filtrates evaporated *in vacuo*. The residue was partitioned between chloroform-sodium carbonate solution (10%), the organic layer removed, the aqueous phase saturated with salt and further extracted with chloroform. The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated *in vacuo* to yield 4-amino-6,7-dimethoxy-2-(piperazin-1-yl)quinoline (2.42 g). Spectroscopy showed this product to be the same as that of Example 20.

The following Preparations illustrate the preparation of certain starting materials.

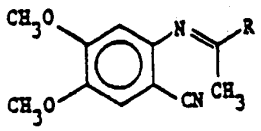
Preparation 1

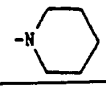
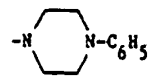
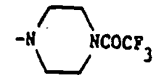
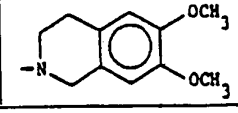


Phosphorous oxychloride (1.0 ml) was added to a stirred solution of dimethylacetamide (2.8 ml) in chloroform (10 ml) at room temperature. The mixture was stirred for 5 minutes, 2-cyano-4,5-dimethoxyaniline (1.78 g) added and the reaction stirred under reflux for 4 hours. The mixture was cooled, poured onto ice and extracted with chloroform and the organic phase discarded. The aqueous layer was basified (solid NaOH) extracted with chloroform, the combined extracts washed with water, dried (Na_2SO_4) and evaporated *in vacuo*. A sample of the brown oily residue (2 g) was crystallised from diisopropylether to give N,N-dimethyl-N'-(2-cyano-4,5-dimethoxyphenyl)acetamidine, m.p. 94—96°.

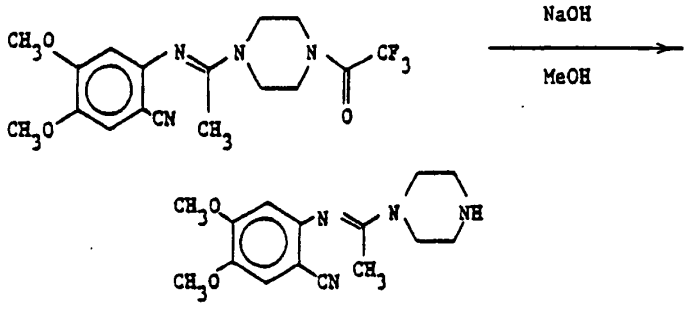
Analysis %:—
Found: C, 63.3; H, 6.9; N, 17.2
Calculated for $C_{13}H_{17}N_3O_2$: C, 63.1; H, 6.9; N, 17.0.

The following compounds were prepared by the same general method as Preparation 1, starting from the appropriate acetyl derivative of the formula $R.COCH_3$. In Preparation 2 the crude product was purified by column chromatography.



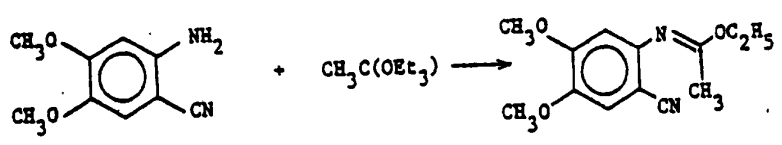
Preparation No.	R	Form Isolated m.p.	Molecular Formula	Analysis % (Theoretical in brackets) C	H	N
2		crude		Characterised by spectroscopy		
3		free base 108—109°	$C_{21}H_{24}N_4O_2$	69.2 (69.2	6.7 6.6	15.3 15.4)
4		free base 136—138°	$C_{17}H_{19}N_4O_3F_3$	52.9 (53.1	4.9 5.0	14.7 14.6)
5		free base 143—145°	$C_{22}H_{25}N_3O_4$	66.0 (66.8	6.3 6.4	10.5 10.6)

Preparation 6



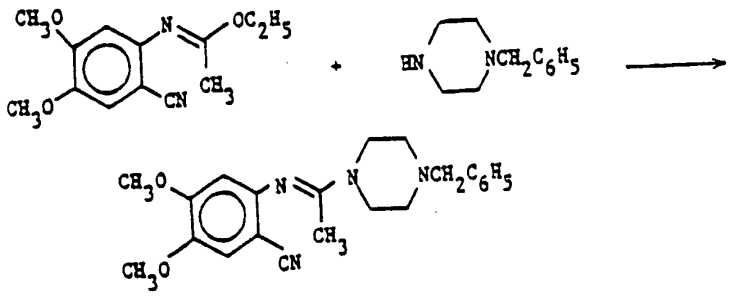
A solution of N-[1-(4-trifluoroacetylpiperazin-1-yl)ethylidene]-2-cyano-4,5-dimethoxyaniline (29.5 g) in methanol (400 ml) and sodium hydroxide (2N, 100 ml) was stirred at room temperature for 3 hours. The mixture was then evaporated *in vacuo*, the residue taken up in chloroform (350 ml) washed with water and dried (Na_2SO_4). The solution was evaporated *in vacuo* and the crude N-(1-[piperazin-1-yl]ethylidene)-2-cyano-4,5-dimethoxyaniline (23 g), used without further purification.

Preparation 7



2-Cyano-4,5-dimethoxyaniline (20 g), a trace of the corresponding hydrogen chloride salt (200 mg) and triethylorthoacetate (40 ml) were stirred at 150° for 1 hour, with removal of ethanol by distillation. The mixture was then evaporated *in vacuo* and the crude residue of ethyl N-(2-cyano-4,5-dimethoxyphenyl)-acetamidate (27.95 g) used directly.

Preparation 8

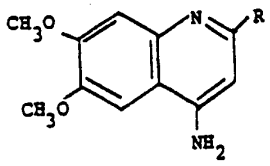


The crude product (26.9 g) from the previous Preparation, N-benzylpiperazine (21 g) and p-toluenesulphonic acid (100 mg) were stirred together at 150° for 2 hours under a slight pressure reduction. On cooling, the residue was taken up in methylene chloride and extracted with dilute hydrochloric acid (2N, 2 × 200 ml). The acid layer was adjusted to pH4 (5N NaOH), extracted with methylene chloride (2 × 200 ml) and the combined extracts discarded. The aqueous phase was then basified to pH9, extracted with methylene chloride (3 × 200 ml), the combined extracts washed with brine, dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by column chromatography (Merck 9385 silica, 400 g) eluting with methylene chloride/methanol (100:0 → 98:2) and a sample of the product (11.68 g) was taken up in ethyl acetate-methanol and treated with ethereal hydrogen chloride. The solid was treated with ether and dried to give N-[1-(4-benzylpiperazin-1-yl)ethylidene]-2-cyano-4,5-dimethoxyaniline dihydrochloride hydrate, m.p. 181—182°.

Analysis %:—
Found: C, 56.6; H, 6.7; N, 11.9
Calculated for $C_{22}H_{26}N_4O_2 2HCl.H_2O$: C, 56.3; H, 6.4; N, 11.9.

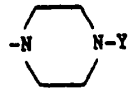
Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

1. A compound of the formula:—



--- (I)

or a pharmaceutically acceptable acid addition salt thereof, wherein R is —N(C_1—C_4 alkyl)$_2$, piperidino, 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinol-2-yl or a group of the formula



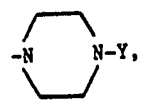
where Y is H, C_1—C_6 alkyl, aryl or C_1—C_4 alkyl substituted by aryl, or Y is selected from

(a) —COR^1 where R^1 is a C_1—C_6 alkyl, C_1—C_4 alkyl substituted by aryl, C_3—C_6 cycloalkyl, (C_3—C_6 cycloalkyl)methyl, aryl, styryl, 2-furyl, 2-tetrahydrofuryl, 2-benzo-1,4-dioxanyl, 2-chromanyl, 5-methylthio-2-(1,3,4-oxadiazolyl) or 2-quinolyl group;

(b) —CONHR^2 where R^2 is C_1—C_6 alkyl, aryl, C_1—C_4 alkyl substituted by aryl, (C_2—C_4 alkenyl)methyl, C_3—C_6 cycloalkyl or (C_3—C_6 cycloalkyl)methyl; and

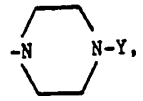
(c) —COOR^3 where R^3 is C_1—C_6 alkyl, C_1—C_4 alkyl substituted by aryl, C_2—C_4 alkyl substituted other than on an α-carbon atom by hydroxy, C_3—C_6 cycloalkyl, (C_3—C_6 cycloalkyl)methyl, (C_2—C_4 alkenyl)methyl, or aryl; aryl, wherever it occurs, meaning phenyl, naphthyl or phenyl substituted by 1 or 2 substituents each selected fr m halo, CF_3, C_1—C_4 alkyl and C_1—C_4 alkoxy, or by a single methyl nedioxy group.

2. A compound according to claim 1, in which R is



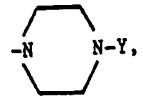
Y is —COR^1 and R^1 is 2-furyl, benzodioxan-2-yl, chroman-2-yl, phenyl, *p*-fluorophenyl, 3,4-methylenedioxyphenyl, methyl, cyclopropylmethyl, cyclopentyl, styryl, 2-naphthyl or 2-quinolyl.

3. A compound according to claim 1, in which R is



Y is —$CONHR^2$ and R^2 is phenyl, cyclopropylmethyl, benzyl, *n*-propyl or allyl.

4. A compound according to claim 1, in which R is



Y is $COOR^3$ and R^3 is ethyl, *iso*butyl, 2-hydroxy-2-methylpropyl, cyclopropylmethyl, *p*-fluorophenyl, benzyl or 2-methylallyl.

5. 4-Amino-2-[4-(2-furoyl)piperazin-1-yl]-6,7-dimethoxyquinoline and its pharmaceutically acceptable acid addition salts.

6. 4-Amino-2-[4-(1,4-benzodioxan-2-carbonyl)piperazin-1-yl]-6,7-dimethoxyquinoline and its pharmaceutically acceptable acid addition salts.

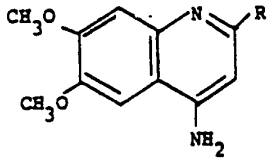
7. 4-Amino-6,7-dimethoxy-2-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinol-2-yl)quinoline and its pharmaceutically acceptable acid addition salts.

8. A pharmaceutical composition comprising a compound as claimed in any of claims 1 to 7 and a pharmaceutically acceptable carrier material.

9. A compound as claimed in claim 1, for use in treating hypertension.

Claims for the Contracting State: AT

1. A process for preparing a compound of the formula:



--- (I)

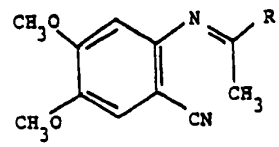
or a pharmaceutically acceptable acid addition salt thereof, wherein R is —$N(C_1—C_4$ alkyl$)_2$, piperidino, 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinol-2-yl or a group of the formula

where Y is H, $C_1—C_6$ alkyl, aryl or $C_1—C_4$ alkyl substituted by aryl, or Y is selected from

(a) —COR^1 where R^1 is a $C_1—C_6$ alkyl, $C_1—C_4$ alkyl substituted by aryl, $C_3—C_6$ cycloalkyl, ($C_3—C_6$ cycloalkyl)methyl, aryl, styryl, 2-furyl, 2-tetrahydrofuryl, 2-benzo-1,4-dioxanyl, 2-chromanyl, 5-methylthio-2-(1,3,4-oxadiazolyl) or 2-quinolyl group;

(b) —$CONHR^2$ where R^2 is $C_1—C_6$ alkyl, aryl, $C_1—C_4$ alkyl substituted by aryl, ($C_2—C_4$ alkenyl)methyl, $C_3—C_6$ cycloalkyl or ($C_3—C_6$ cycloalkyl)methyl; and

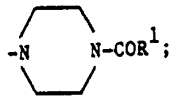
(c) —$COOR^3$ where R^3 is $C_1—C_6$ alkyl, $C_1—C_4$ alkyl substituted by aryl, $C_2—C_4$ alkyl substituted other than on an α-carbon atom by hydroxy, $C_3—C_6$ cycloalkyl, ($C_3—C_6$ cycloalkyl)methyl, ($C_2—C_4$ alkenyl)methyl, or aryl; aryl, wherever it occurs, meaning phenyl, naphthyl or phenyl substituted by 1 or 2 substituents each selected from halo, CF_3, $C_1—C_4$ alkyl and $C_1—C_4$ alkoxy, or by a single methylenedioxy group, which comprises cyclising a compound of the formula:



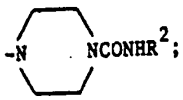
wherein R is as already defined; then, if necessary, carrying out any one or more of the following steps:

(i) debenzylating a product of formula (I) in which R is 4-benzyl-piperazin-1-yl to form a compound in which R is piperazino;

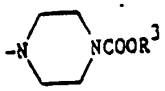
(ii) acylating a product of formula (I) in which R is piperazino, with a compound of the formula R^1COQ in which Q is a facile leaving group, to form a compound in which R is



(iii) reacting a product of formula (I) in which R is piperazino, with an isocyanate of the formula $R^2.NCO$ or a carbamoyl chloride of the formula $R^2.NHCOCl$, to form a compound in which R is



(iv) reacting a product of formula (I) in which R is piperazino, with a compound of the formula R^3OCOQ in which Q is a facile leaving group, to form a compound in which R is



or

and then, if desired, converting the product to a pharmaceutically acceptable acid addition salt thereof.

2. A process according to claim 1 including step (ii), in which R is piperazino or 4-benzyl-piperazin-1-yl and R^1 is a 2-furyl group.

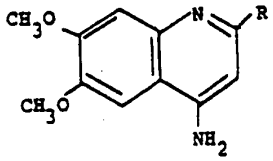
3. A process according to claim 1 including step (ii), in which R is piperazino or 4-benzyl-piperazin-1-yl and R^1 is a benzo-1,4-dioxan-2-yl group.

4. A process according to claim 1 including step (iv), in which R is piperazino or 4-benzyl-piperazin-1-yl and R^3 is an alkenyl-methyl group, wherein the product is further reacted with concentrated sulphuric acid to form a compound in which R^3 is a hydroxyalkyl-methyl group, and then, if desired, converting the product to a pharmaceutically acceptable acid addition salt.

5. A process according to claim 1 in which R is a 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl group.

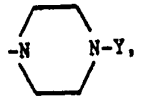
Patentansprüche für die Vertragsstaaten: BE CH DE FR GB IT LI LU NL SE

1. Verbindung der Formel



--- (I)

oder ein pharmazeutisch annehmbares Säureadditionssalz derselben, worin R $—N(C_1—C_4\text{-Alkyl})_2$, Piperidino, 6,7-Dimethoxy-1,2,3,4-tetrahydroisochinol-2-yl oder eine Gruppe der Formel



worin Y H, $C_1—C_6$-Alkyl, Aryl oder $C_1—C_4$-Alkyl, substituiert durch Aryl, ist, oder Y ausgewählt ist aus

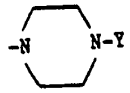
(a) $—COR^1$, worin R^1 $C_1—C_6$-Alkyl, $C_1—C_4$-Alkyl, substituiert durch Aryl, $C_3—C_6$-Cycloalkyl, ($C_3—C_6$-Cycloalkyl)methyl, Aryl, Styryl, 2-Furyl, 2-Tetrahydr furyl, 2-Benzo-1,4-dioxanyl, 2-Chromanyl, 5-Methylthi -2-(1,3,4-oxodiazolyl) d r ein 2-Chinolylgruppe ist;

(b) $—CONHR^2$, w rin R^2 $C_1—C_6$-Alkyl, Aryl, $C_1—C_4$-Alkyl, substitui rt durch Aryl, ($C_2—C_4$-Alkenyl)methyl, $C_3—C_6$-Cycloalkyl od r ($C_3—C_6$-Cycl alkyl)methyl ist; und

(c) $—COOR^3$, worin R^3 $C_1—C_6$-Alkyl, $C_1—C_4$-Alkyl, substituiert durch Aryl, $C_2—C_4$-Alkyl, anders substituiert als am α-Kohlenstoffatom durch Hydroxy, $C_3—C_6$-Cycloalkyl, ($C_3—C_6$-Cycloalkyl)methyl, ($C_2—C_4$-Alkenyl)methyl oder Aryl ist;

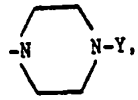
wobei Aryl, wo immer es auftritt, Phenyl, Naphthyl oder Phenyl, substituiert durch 1 oder 2 Substituenten, jeweils ausgewählt aus Halogen, CF_3, C_1—C_4-Alkyl und C_1—C_4-Alkoxy, oder durch eine einzige Methylendioxygruppe, bedeutet, ist.

2. Verbindung gemäß Anspruch 1, in welcher R



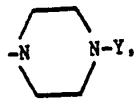
ist, Y —COR^1 ist und R^1 2-Furyl, Benzodioxan-2-yl, Chroman-2-yl, Phenyl, p-Fluorphenyl, 3,4-Methylendioxyphenyl, Methyl, Cyclopropylmethyl, Cyclopentyl, Styryl, 2-Naphthyl oder 2-Chinolyl ist.

3. Verbindung gemäß Anspruch 1, in welcher R



ist, Y —$CONHR^2$ ist und R^2 Phenyl, Cyclopropylmethyl, Benzyl, n-Propyl oder Allyl ist.

4. Verbindung gemäß Anspruch 1, in welcher R



ist, Y $COOR^3$ ist und R^3 Ethyl, i-Butyl, 2-Hydroxy-2-methylpropyl, Cyclopropylmethyl, p-Fluorphenyl, Benzyl oder 2-Methylallyl ist.

5. 4-Amino-2-[4-(2-furoyl)piperazin-1-yl]-6,7-dimethoxychinolin und dessen pharmazeutisch annehmbare Säureadditionssalze.

6. 4-Amino-2-[4-(1,4-benzodioxan-2-carbonyl)piperazin-1-yl)-6,7-dimethoxychinolin und dessen pharmazeutisch annehmbare Säureadditionssalze.

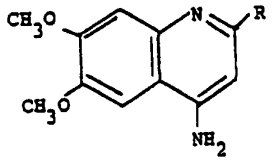
7. 4-Amino-6,7-dimethoxy-2-(6,7-dimethoxy-1,2,3,4-tetrahydroisochinol-2-yl)chinolin und dessen pharmazeutisch annehmbare Säureadditionssalze.

8. Pharmazeutische Zusammensetzung, umfassend eine Verbindung, wie sie in irgendeinem der Ansprüche 1 bis 7 beansprucht wird, und ein pharmazeutisch annehmbares Trägermaterial.

9. Verbindung gemäß Anspruch 1 zur Verwendung bei der Behandlung der Hypertension.

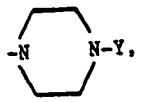
Patentansprüche für den Vertragsstaat: AT

1. Verfahren zur Herstellung einer Verbindung der Formel



--- (I)

oder eines pharmazeutisch annehmbaren Säureadditionssalzes hiervon, worin R —$N(C_1$—C_4-Alkyl$)_2$, Piperidino, 6,7-Dimethoxy-1,2,3,4-tetra-hydroisochinol-2-yl oder eine Gruppe der Formel

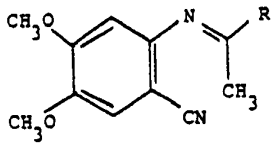


ist worin Y H, C_1—C_6-Alkyl, Aryl oder C_1—C_4-Alkyl, substituiert durch Aryl, ist, oder Y ist ausgewählt aus

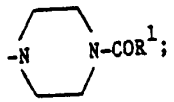
(a) —COR^1, worin R^1 C_1—C_6-Alkyl, C_1—C_4-Alkyl, substituiert durch Aryl, C_3—C_6-Cycloalkyl, (C_3—C_6-Cycloalkyl)m thyl, Aryl, Styryl, 2-Furyl, 2-Tetrahydrofuryl, 2-Benzo-1,4-dioxanyl, 2-Chromanyl, 5-Methylthio-2-(1,3,4-oxadiazolyl) oder eine 2-Chinolylgruppe ist;

(b) —$CONHR^2$, worin R^2 C_1—C_6-Alkyl, Aryl, C_1—C_4-Alkyl, substituiert durch Aryl, (C_2—C_4-Alkenyl)methyl, C_3—C_6-Cycloalkyl oder C_3—C_6-Cycloalkyl)methyl ist; und

(c) —$COOR^3$, worin R^3 C_1—C_6-Alkyl, C_1—C_4-Alkyl, substituiert durch Aryl, C_2—C_4-Alkyl, anders substituiert als am α-Kohlenstoffatom durch Hydroxy, C_3—C_6-Cycloalkyl, (C_3—C_6-Cycloalkyl)methyl, (C_2—C_4-Alkenyl)methyl oder Aryl ist,
wobei Aryl, wo immer es auftritt, Phenyl, Naphthyl oder Phenyl, substituiert durch 1 oder 2 Substituenten, jeweils ausgewählt aus Halogen, CF_3, C_1—C_4-Alkyl und C_1—C_4-Alkoxy, oder durch eine einzige Methylendioxygruppe, bedeutet, dadurch gekennzeichnet, daß eine Verbindung der Formel

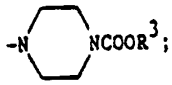


worin R wie zuvor definiert ist, cyclisiert, dann, wenn nötig, eine oder mehrere der folgenden Stufen durchgeführt wird:
(i) Debenzylieren eines Produkts der Formel (I), worin R 4-Benzyl-piperazin-1-yl ist, zu einer Verbindung, worin R Piperazino ist,
(ii) Acylieren eines Produkts der Formel (I), worin R Piperazino ist, mit einer Verbindung der Formel R^1COQ, worin Q eine leicht austretende Gruppe ist, zu einer Verbindung, worin R



ist,
(iii) Umsetzen eines Produkts der Formel (I), worin R Piperazino ist, mit einem Isocyanat der Formel R^2NCO oder einem Carbamoylchlorid der Formel $R^2NHCOCl$ zu einer Verbindung, worin R

ist,
(iv) Umsetzen eines Produkts der Formel (I), worin R Piperazino ist, mit einer Verbindung der Formel R^3OCOQ, worin Q eine leicht austretende Gruppe ist, zu einer Verbindung, worin R



ist,
und dann, wenn gewünscht, Umwandeln des Produkts in ein pharmazeutisch annehmbares Säureadditionssalz.

2. Verfahren nach Anspruch 1 mit Stufe (ii), in welchem R Piperazino oder 4-Benzyl-piperazin-1-yl und R^1 eine 2-Furylgruppe ist.

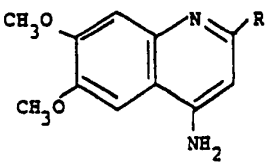
3. Verfahren nach Anspruch 1 mit Stufe (ii), in welchem R Piperazino oder 4-Benzyl-piperazin-1-yl und R^1 eine Benzo-1,4-dioxan-2-yl-Gruppe ist.

4. Verfahren nach Anspruch 1 mit Stufe (iv), in welchem R Piperazino oder 4-Benzyl-piperazin-1-yl und R^3 eine Alkenyl-methylgruppe ist, worin das Produkt ferner mit konzentrierter Schwefelsäure zu einer Verbindung, worin R^3 eine Hydroxyalkyl-methylgruppe ist, umgesetzt und dann, wenn gewünscht, das Produkt in ein pharmazeutisch annehmbares Säureadditionssalz umgewandelt wird.

5. Verfahren nach Anspruch 1, in welchem R eine 6,7-Dimethoxy-1,2,3,4-tetrahydroisochinolin-2-ylgruppe ist.

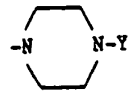
Revendications pour les Etats contractants: BE CH DE FR GB IT LI LU NL SE

1. Composé de formule



--- (I)

ou sel d'addition acide pharmaceutiquement acceptable d'un tel composé, formule dans laquelle R représénte un groupe —N(alkyle en C_1—C_4)$_2$, pipéridino, 6,7-diméthoxy-1,2,3,4-tétrahydroisoquinol-2-yle ou un groupe de formule



dans laquelle Y représente H, alkyle en C_1—C_6, aryle ou alkyle en C_1—C_4 substitué par un groupe aryle, ou Y est choisi entre:

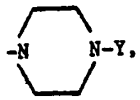
(a) —COR^1 dans laquelle R^1 est un groupe alkyle en C_1—C_6, alkyle en C_1—C_4 substitué par un groupe aryle, cycloalkyle en C_3—C_6, (cycloalkyl en C_3—C_6)méthyle, aryle, styryle, 2-furyle, 2-tétrahydrofuryle, 2-benzo-1,4-dioxanyle, 2-chromanyle, 5-méthylthio-2-(1,3,4-oxadiazolyle) ou 2-quinolyle:

(b) —$CONHR^2$ dans laquelle R^2 représente un groupe alkyle en C_1—C_6, aryle, alkyle en C_1—C_4 substitué par un groupe aryle, (alkényle en C_2—C_4)méthyle, cycloalkyle en C_3—C_6 ou (cycloalkyle en C_3—C_6)méthyle; et

(c) —$COOR^3$ dans laquelle R^3 est un groupe alkyle en C_1—C_6, alkyle en C_1—C_4 substitué par un groupe aryle, alkyle en C_2—C_4 substitué sur un atome de carbone autre que l'atome de carbone en α par un groupe hydroxy, cycloalkyle en C_3—C_6, (cycloalkyle en C_3—C_6)méthyle, (alkényle en C_2—C_4)méthyle, ou aryle;

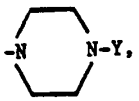
le terme aryle, lorsqu'il est utilisé, signifiant phényle, naphtyle ou phényle substitué par un ou deux substituants dont chacun est choisi parmi les groupes halogéno, CF_3, alkyle en C_1—C_4 et alcoxy en C_1—C_4 ou par un groupe méthylènedioxy unique.

2. Composé selon la revendication 1, dans lequel R représente



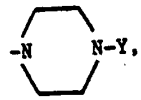
Y représente COR^1 et R^1 représente un groupe 2-furyle, benzodioxane-2-yle, chroman-2-yle, phényle, p-fluorophényle, 3,4-méthylènedioxyphényle, méthyle, cyclopropylméthyle, cyclopentyle, styryle, 2-naphtyle ou 2-quinolyle.

3. Composé selon la revendication 1, dans lequel R représente



Y représente —$CONHR^2$ et R^2 représente un groupe phényle, cyclopropylméthyle, benzyle, n-propyle ou allyle.

4. Composé selon la revendication 1, dans lequel R représente



Y représente $COOR^3$ et R^3 représente un groupe éthyle, isobutyle, 2-hydroxy-2-méthylpropyle, cyclopropylméthyle, *p*-fluorophényle, benzyle ou 2-méthylallyle.

5. 4-Amino-2-(4-2-(furoyl)pipérazin-1-yl)-6,7-diméthoxyquinoline et ses sels d'addition acide pharmaceutiquement acceptables.

6. 4-Amino-2-(4-1,4-(benzodioxan-2-carbonyl)pipérazin-1-yl)-6,7-diméthoxyquinoline et ses sels d'addition acide pharmaceutiquement acceptables.

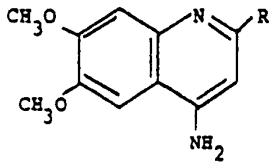
7. 4-amino-6,7-diméthoxy-2-(6,7-diméthoxy-1,2,3,4-tétrahydroisoquinol-2-yl)quinoline et ses sels d'addition acide pharmaceutiquement acceptables.

8. Composition pharmaceutique comprenant un composé selon l'une quelconque des revendications 1 à 7 et un matériau support pharmaceutiquement acceptable.

9. Composé selon la revendication 1 pour son utilisation dans le traitement de l'hypertension.

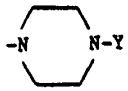
Revendications pour l'Etat contractant: AT

1. Procédé de préparation d'un composé de formule



--- (I)

ou d'un sel d'addition acide pharmaceutiquement acceptable d'un tel composé, formule dans laquelle R représente un groupe —N(alkyle en C_1—C_4)$_2$, pipéridino, 6,7-diméthoxy-1,2,3,4-tétrahydroisoquinol-2-yle ou un groupe de formule



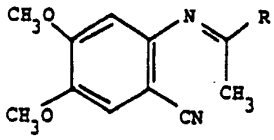
dans laquelle Y représente H, alkyle en C_1—C_6, aryle ou alkyle en C_1—C_4 substitué par un groupe aryle, ou Y est choisi entre:

(a) —COR^1 dans laquelle R^1 est un groupe alkyle en C_1—C_6, alkyle en C_1—C_4 substitué par un groupe aryle, cycloalkyle en C_3—C_6, (cycloalkyl en C_3—C_6)méthyle, aryle, styryle, 2-furyle, 2-tétrahydrofuryle, 2-benzo-1,4-dioxanyle, 2-chromanyle, 5-méthylthio-2-(1,3,4-oxadiazolyle) ou 2-quinolyle:

(b) —CONHR^2 dans laquelle R^2 représente un groupe alkyle en C_1—C_6, aryle, alkyle en C_1—C_4 substitué par un groupe aryle, (alkényle en C_2—C_4)méthyle, cycloalkyle en C_3—C_6 ou (cycloalkyle en C_3—C_6)méthyle; et

(c) —COOR^3 dans laquelle R^3 est un groupe alkyle en C_1—C_6, alkyle en C_1—C_4 substitué par un groupe aryle, alkyle en C_2—C_4 substitué sur un atome de carbone autre que l'atome de carbone en α par un groupe hydroxy, cycloalkyle en C_3—C_6, (cycloalkyle en C_3—C_6)méthyle, (alkényle en C_2—C_4)méthyle, ou aryle;

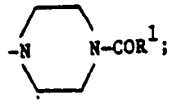
le terme aryle, lorsqu'il est utilisé, signifiant phényle, naphtyle ou phényle substitué par un ou deux substituants dont chacun est choisi parmi les groupes halogéno, CF_3, alkyle en C_1—C_4 et alcoxy en C_1—C_4 ou par un groupe méthylènedioxy unique, qui consiste à cycliser un compose de formule:



dans laquelle R est tel que précédemment défini; puis, si nécessaire, à metrre en oeuvre une ou plusieurs des étapes suivantes:

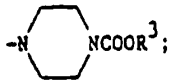
(i) débenzylation d'un produit de formule (I) dans lequel R est un groupe 4-benzyl-pipérazin-1-yl pour former un composé dans lequel R est un groupe pipérazino;

(ii) acylation d'un produit de formule (I) dans lequel R est un groupe pipérazino, avec un composé de formule R^{1}COQ dans laquelle Q est un groupe facilement labile, pour former un composé dans lequel R représente



(iii) réaction d'un composé de formule (I) dans laquelle R représente un groupe pipérazino, avec un isocyanate de formule R^2.NCO ou un chlorure de carbamoyle de formule R^{2}NHCOCl, pour former un composé dans lequel R représente

(iv) réaction d'un composé de formule (I) dans laquelle R est un group pipérazino avec un composé de formule R^3OCOQ dans laquelle Q est un groupe facilement labile, pour former un composé dans lequel R est un groupe



ensuite, si on le désire, à transformer le produit en sel d'addition acide pharmaceutiquement acceptable de ce dernier.

2. Procédé selon la revendication 1, comprenant l'étape (ii), avec R représentant un groupe pipérazino ou 4-benzyl-pipérazin-1-yle et R^1 représentant un groupe 2-furyle.

3. Procédé selon la revendication 1, comprenant l'étape (ii), avec R représentant un groupe pipérazino ou 4-benzyl-pipérazin-1-yle et R^1 représentant un groupe benzo-1,4-dioxan-2-yle.

4. Procédé selon la revendication 1, comportant l'étape (iv), avec R représentant un groupe pipérazino ou 4-benzyl-pipérazin-1-yle et R^3 représentant un groupe alkénylméthyle, procédé selon lequel on fait ensuite réagir le produit avec de l'acide sulfurique concentré pour former un composé dans lequel R^3 est un groupe hydroxyalkyl-méthyle puis, si on le désire, on transforme le produit en un sel d'addition acide pharmaceutiquement acceptable.

5. Procédé selon la revendication 1, dans lequel R représente un groupe 6,7-diméthoxy-1,2,3,4-tétrahydroisoquinolin-2-yle.